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Review

Biocontrol for environmental control of the human parasite, *Strongyloides stercoralis*: A necessary next step

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HIGHLIGHTS

- *Strongyloides stercoralis* presents a key challenge to Australian indigenous health.
- Currently Strongyloidiasis treatment relies upon administration of anthelminthics.
- Biological control is incorporated into management of Malaria.
- Nematophagous fungi should be incorporated into *S. stercoralis* management.

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ABSTRACT

Strongyloides stercoralis is a human parasitic nematode that infects 100–370 million people globally; prevalence comparable to malaria. Currently the primary treatment for strongyloidiasis is the anthelminthic drug, ivermectin. The ruminant variant of *S. stercoralis* (*Strongyloides papillosus*) has been shown to be resistant to ivermectin. Efforts to control *S. stercoralis* therefore must extend beyond clinical treatment. A similar approach to that taken by integrated pest management systems should be taken with this disease, including biological control. Malaria is an example of integrated pest management and multiple biocontrol approaches.

The use of nematophagous fungi is widespread in agricultural control of nematodes. A review of the literature demonstrates that nematophagous fungi to control *Strongyloides stercoralis* could be an effective approach. Here we argue that developing biocontrol methods to control *S. stercoralis* is important as multiple approaches to complicated diseases creates a more robust approach to disease control.

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1. Introduction

1.1. Biocontrol

Biological control or biocontrol is a pest or disease management system that uses one organism to control another. It is often used in an agricultural setting where a crop disease is controlled by a natural predator. Biocontrol is becoming an increasingly popular approach to managing livestock disease, particularly against parasitic nematodes (Larsen, 1999). The veterinary literature is now abundant with reports of anthelminthic resistance including ivermectin (Waller and Larsen, 1993) meaning other control measures, particularly those using an environmental approach as opposed to a clinical one, are gaining recognition. Biocontrol of human diseases has been investigated and must be included in disease management programs. *Strongyloides stercoralis* is a parasitic nematode that infects humans and is currently treated only by anthelminthic drugs. This sole treatment option is of concern as the ruminant variant of *Strongyloides* (*S. papillosus*) has been shown to be resistant to ivermectin. A similar approach to that taken by integrated pest management systems should be taken to this disease, which should include biological control.

1.2. Nematodes

Free living nematodes play an important role in soil health, nutrient recycling and adding to the biodiversity of the environments in which they inhabit (Neher, 2010). Notwithstanding, the spectrum of problems that can be caused by nematodes in the environment is broad, including agricultural pest nematodes and human parasitic nematodes which impact upon agricultural and human health respectively (Nicol et al., 2011; Hotez, 2008). Nematodes cause a range of crop diseases such as root rot disease, cereal cyst disease, root lesion, stem nematode disease and seed gall nematode disease. These nematodes impact on a broad range of crops including cereal crops, vegetable, pastures and grasses. Agriculturally significant pest nematodes also include veterinary nematode diseases. Some examples are *Strongyloides papillosus* which infects cattle, sheep and goats (Chandrawathani et al., 1998), *Strongyloides westeri* which infects equine species (Araujo et al., 2010), *Dictyocaulus viviparous* which infects cattle (Pezzementi et al., 2012), *Muellerius capillaris* which infects sheep (Viña et al., 2013) and *Metastrongylus* spp. which infects pigs (Alvarez et al., 2013).

Human health is also affected by nematodes with many parasitic species endemic particularly in tropical regions of the world. Some common human parasitic nematode diseases include Ascariasis (*Ascaris lumbricoides*), Trichuriasis (*Trichuris trichiura*) also known as whipworm, and Strongyloides (*Strongyloides stercoralis*) (Bethony et al., 2006; Rayan et al., 2012). Currently control of these parasites relies almost entirely upon clinical intervention once infection has already occurred.

1.3. Nematophagous fungi

There is now a large body of research assessing new biocontrol organisms and their modes of action (Morton et al., 2004; Lopez-Llorca et al., 2008). It is expected that there will be significant growth in the bio-pesticide market in years to come (Vos et al., 2014). One important biocontrol technique is the use of nematophagous fungi. Nematophagous fungi reside in moist soil environments and are capable of trapping and digesting nematodes. Predated nematodes are used to supplement low nutrients in some soil environments; nematodes predominantly provide an additional source of nitrogen (Nordbring-Hertz et al., 2006). There are multiple types of nematophagous fungi and they affect different parts of a nematode's lifecycle. The fungi can parasitise the eggs, the reproductive tract of an adult nematode or physically trap larvae or adult worms through constricting rings, adhesive nets, adhesive knobs or adhesive spores along with many other methods (Nordbring-Hertz et al., 2006). These multiple modes of action, together with little or no evidence of developed resistance, makes nematophagous fungi an obvious choice for biocontrol to supplement control using antihelminthics.

If resistance to human anthelminthics develops as has been seen in agricultural settings, environmental control might be one of the few tools left in our arsenal against nematodes.

2. Nematophagous fungi and biocontrol in agricultural crops

Chemical nematicides are toxic by design. Methyl bromide is a nematicide that is now recognised as an ozone depleting agent and has been phased out by most countries (Margolis et al., 2013). Carbofuran is a nematicide that is highly toxic to humans and other organisms (Gupta, 1994) in addition to the target pests (Otieno et al., 2010). It has been banned or restricted in several countries including Canada and the U.S. (Otieno et al., 2010). With few safe, degrading nematicidal options available, there is a need for a better alternative. The number and spread of nematode diseases has been increasing, with a concomitant impact on the agricultural industry (Nicol et al., 2011). Nematodes affect a broad range of crops resulting in effects on the production cost and quality of a large number of food products (Nicol et al., 2011). This reduces crop yields and increases the costs of measures that must take place to reduce nematode disease. Plant parasitic nematodes have been estimated to cost up to USD$358 billion per year worldwide due to yield losses (Askary, 2015).

Nematophagous fungi have been investigated as a safer and less environmentally destructive alternative to these chemicals. Nematophagous fungi also have the ability to persist and grow in soils unlike chemicals requiring repeated applications. There has been success in this research field with several fungal species available commercially such as *Paecilomyces lilacinus* (Melocon® or Bio Act®). These have efficacy comparable to chemical nematicides (Schenck, 2003). *P. lilacinus* was shown to be up to 98.7% effective at parasitizing root rot nematode *Meloidogyne incognita* eggs in vitro (Aminuzzaman et al., 2012). *P. lilacinus* has also shown to be effective on *Meloidogyne javanica* in tomatoes (Kiewnick and Sikora, 2006).

The application of this nematophagous fungus is one of many examples of biological control successes, and serves to increase momentum for research into other areas of agriculture, conservation and human health.

3. Human health and biocontrol

Biological control has successfully been used with various human parasitic diseases. Notably, biological control has targeted vectors involved in the transmission process. Examples of this are mosquito transmitted diseases such as malaria, tsetse fly transmitted diseases such as human trypanosomiasis and tick transmitted disease such as Lyme disease. With malaria, biological control mechanisms disrupt the mosquito phase of the malaria transmission cycle. Mermithid nematodes are aquatic nematodes that parasitise arthropods, including mosquitos (Platzer, 2007). The juvenile nematode enters the host via penetration of the external cuticle, obtaining nutrients and killing the host on exit (Platzer, 2007). Entomopathogenic fungi infect adult mosquitoes via direct contact with the external cuticle (ingestion is not required) (Kamareddine, 2012) (Mnyone et al., 2012). The fungus kills the mosquito after infection. The kill rate is slower than that of insec-